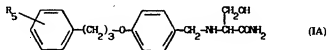
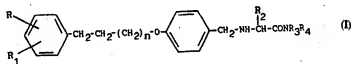




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(54) Title: SUBSTITUTED (ARYLALKOXYBENZYL)AMINOPROPANAMIDE DERIVATIVES, THEIR PREPARATION AND USE AS ANTI-EPILEPTIC, NEUROPROTECTIVE AND ANTIDEPRESSANT AGENTS



(57) Abstract

The invention provides new compounds of formula (I) wherein, subject to a proviso, n is zero or an integer of 1 to 3; each of R and R₁, which may be the same or different, is hydrogen, halogen, trifluoromethyl or C₁-C₄ alkoxy; R₂ is hydrogen or C₁-C₄ alkyl optionally substituted by hydroxy; each of R₃ and R₄ independently is hydrogen or C₁-C₄ alkoxy; or a pharmaceutically acceptable salt thereof; and of formula (IA), wherein R₃ is hydrogen, halogen, trifluoromethyl or C₁-C₄ alkoxy, or a pharmaceutically acceptable salt thereof, which are active on the central nervous system (CNS) and can be used in therapy as anti-epileptics, anti-Parkinson, neuroprotective, antidepressant, anti-spastic and hypnotic agents.

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SUBSTITUTED (ARYLALKOXYBENZYL) AMINOPROPANAMIDE DERIVATIVES,
THEIR PREPARATION AND USE AS ANTI-EPILEPTIC,
NEUROPROTECTIVE AND ANTIDEPRESSANT AGENTS

The present invention relates to substituted
5 (phenylalkoxybenzyl)aminopropanamide derivatives, to
their use as therapeutic agents, to a process for their
preparation and to pharmaceutical compositions containing
them.

Other N-substituted α -amino carboxamide derivatives are
10 known as having pharmacological properties, for instance
those described by British patent No. 1140748. The
compounds according to this prior art document are useful
in the treatment and prophylaxis of such diseases as
coronary artery disease and atherosclerosis; moreover
15 they are useful in the treatment of inflammatory
conditions such as rheumatoid arthritis.

Further substituted amino acid derivatives are known as
enkephalinase inhibitors, analgesics and hypotensives
from EP-A-0038758.

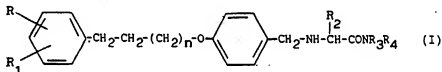
20 Still other substituted glycine and alanine derivatives
are disclosed by US-A-4049663. The compounds according to
this document have utility as oral analgesics.

WO-90/14334 discloses N-phenylalkyl substituted α -
aminocarboxamide derivatives active on the central

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nervous system.

It has now been found that novel substituted (aryl-
alkoxybenzyl)aminopropanamide derivatives as herein
defined have valuable biological properties, in particu-
lar as anti-epileptic, anti-Parkinson, neuroprotective,
antidepressant, antispastic, and/or hypnotic agents.
Accordingly, the present invention provides a new
compound of formula (I)



10 wherein

n is zero or an integer of 1 to 3;

each of R and R₁, which may be the same or different, is
hydrogen, halogen, trifluoromethyl or C₁-C₄ alkoxy;

R₂ is hydrogen or C₁-C₄ alkyl optionally substituted by

15 hydroxy;

each of R₃ and R₄ independently is hydrogen or C₁-C₄
alkyl; or a pharmaceutically acceptable salt thereof; and

wherein when, at the same time, n is zero, 1 or 2, R₂ is
hydrogen or unsubstituted C₁-C₄ alkyl and R and R₁ are as

- 3 -

defined above, then R_3 and R_4 are both hydrogen; and wherein when, at the same time, R and R_1 are hydrogen, n is zero or 1 and R_2 is methyl, then at least one of R_3 and R_4 is other than hydrogen.

- 5 A $-(CH_2)_n-$ group may be a branched or straight alkylene chain.

A halogen atom is preferably fluorine, chlorine or bromine, in particular fluorine or chlorine.

- 10 A C_1-C_4 alkoxy group may be a branched or straight group, typically methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert-butoxy, preferably methoxy or ethoxy.

A C_1-C_4 alkyl group may be a branched or straight group, typically methyl, ethyl, propyl, isopropyl, butyl or tert-butyl, preferably methyl or ethyl.

- 15 A C_1-C_4 alkyl group substituted by hydroxy is typically hydroxymethyl.

Preferred compounds of the invention are the compounds of formula (I) wherein, subject to the above proviso, n is as defined above;

- 20 R is hydrogen and R_1 is hydrogen, halogen or C_1-C_4 alkoxy;

R_2 is C_1-C_4 alkyl;

R_3 and R_4 are hydrogen; and the pharmaceutically acceptable salts thereof.

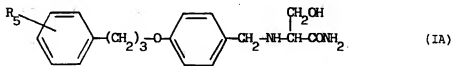
- 25 Specific examples of preferred compounds of the invention

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are:

- 2-[4-(5-phenylpentyl)oxybenzyl]aminopropanamide;
 2-[4-[2-(2-fluorophenyl)ethyl]oxybenzyl]aminopropanamide;
 2-[4-[2-(3-fluorophenyl)ethyl]oxybenzyl]aminopropanamide;
 5 2-[4-(4-phenylbutyl)oxybenzyl]aminopropanamide;
 2-[4-[3-(2-fluorophenyl)propyl]oxybenzyl]aminopropanamide;
 2-[4-[3-(3-fluorophenyl)propyl]oxybenzyl]aminopropanamide;
 2-[4-[3-(4-fluorophenyl)propyl]oxybenzyl]aminopropanamide;
 2-[4-[3-(2-chlorophenyl)propyl]oxybenzyl]aminopropanamide;
 10 2-[4-[3-(3-chlorophenyl)propyl]oxybenzyl]aminopropanamide;
 2-[4-[3-(4-chlorophenyl)propyl]oxybenzyl]aminopropanamide;
 2-[4-[3-(2-bromophenyl)propyl]oxybenzyl]aminopropanamide;
 2-[4-[3-(3-bromophenyl)propyl]oxybenzyl]aminopropanamide;
 2-[4-[3-(2,6-dichlorophenyl)propyl]oxybenzyl]aminopropanamide;
 15 2-[4-[3-(3-methoxyphenyl)propyl]oxybenzyl]aminopropanamide;
 2-[4-[3-(2-methoxyphenyl)propyl]oxybenzyl]aminopropanamide;
 2-[4-(3-phenylpropyl)oxybenzyl]amino-3-hydroxy-N-methylpropanamide;
 if the case, either as single (S) or (R) isomer or as a
 mixture thereof; and the pharmaceutically acceptable
 20 salts thereof,

The present invention also provides a compound of the
 following formula (IA)



- 5 -

wherein R_s is hydrogen, halogen, trifluoromethyl or C_1 - C_4 alkoxy; or a pharmaceutically acceptable salt thereof.

Compounds of formula (IA) are a selected class of compounds according to WO-90/14334.

- 5 Preferred compounds of formula (IA) are those wherein R_s is hydrogen or halogen; and the pharmaceutically acceptable salts thereof.

Specific examples of preferred compounds of formula (IA) are the following:

- 10 2-[4-(3-phenylpropyl)oxybenzyl]amino-3-hydroxypropanamide;

2-{4-[3-(2-fluorophenyl)propyl]oxybenzyl}amino-3-hydroxypropanamide;

- 15 2-{4-[3-(3-fluorophenyl)propyl]oxybenzyl}amino-3-hydroxypropanamide;

if the case, either as single (R) or (S) isomer or as a mixture thereof; and the pharmaceutically acceptable salts thereof.

- The compounds of formulae (I) and (IA) and their salts
20 are hereafter referred to as the "active compounds" and as the "compounds of the invention".

- The present invention includes all the possible optical isomers of the compounds of formulae (I) and (IA) and their mixtures, as well as the metabolites thereof. The
25 present invention also includes within its scope

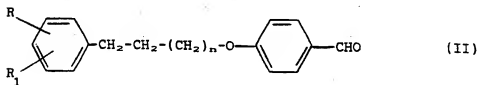
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pharmaceutically acceptable bioprecursors and prodrugs of the compounds of formulae (I) and (IA), i.e. compounds, which have a formula different to formulae (I) and (IA), respectively, but which nevertheless are directly or indirectly converted in vivo into a compound of formulae (I) or (IA), respectively, upon administration to a human being.

Pharmaceutically acceptable salts of the compounds of formulae (I) and (IA) include acid addition salts with inorganic acids, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric, and phosphoric acid, or organic acids, e.g. acetic, propionic, glycolic, lactic, oxalic, malonic, malic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic and salicylic acids.

The compounds of formula (I) and the pharmaceutically acceptable salts thereof can be obtained by a process comprising

a) reacting a compound of formula (II)



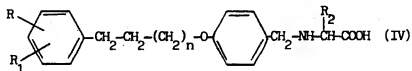
wherein R, R₁ and n are as defined above with a compound of formula (III)

- 7 -



wherein R_2 , R_3 and R_4 are as defined above; or

- b) reacting a compound of formula (IV) or a reactive derivative thereof

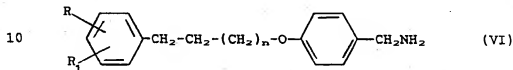


- 5 wherein R , R_1 , n and R_2 are as defined above, with an amine of formula (V)



wherein R_3 and R_4 are as defined above; or

- c) reacting a compound of formula (VI)



10 wherein R , R_1 and n are as defined above, with a

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compound of formula (VII)



5 wherein R_2 , R_3 , and R_4 are as defined above and W is
a halogen atom; and, if desired, converting a
compound of formula (I) into another compound of
formula (I), and/or, if desired, converting a
compound of the invention into a pharmaceutically
acceptable salt and/or, if desired, converting a
10 salt into a free compound and/or, if desired,
separating a mixture of isomers of compounds of the
invention into the single isomers.

All the processes described hereabove are analogy
processes and can be carried out according to well known
15 methods in organic chemistry.

The reaction of a compound of formula (II) with a
compound of formula (III) is a reductive amination
reaction which can be carried out according to well known
methods. According to a preferred embodiment of the
20 invention it may be performed under nitrogen atmosphere,
in a suitable organic solvent, such as an alcohol, e.g.
a lower alkanol, in particular methanol, or in

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acetonitrile, at a temperature ranging from about 0°C to about 40°C, in the presence of a reducing agent, the most appropriate being sodium cyanoborohydride. Occasionally, molecular sieves can be added to the reaction mixture for
5 facilitating the reaction.

A reactive derivative of a compound of formula (IV) may be for instance an alkyl ester thereof, e.g. a C₁-C₆ alkyl ester such as a C₁-C₄ alkyl ester and, in particular a methyl, ethyl or propyl ester, which may be
10 unsubstituted or substituted by a phenyl ring optionally substituted by a nitro group.

Preferably an alkyl ester of a compound of formula (IV) is used.

The reaction of a compound of general formula (IV) or a
15 reactive derivative thereof and an amine of formula (V) can be performed using an excess of the amine, optionally in the presence of water or of an organic solvent, such as dimethylformamide. The temperature of the reaction may range from about 20°C to about 100°C.

20 In a compound of formula (VII) W is preferably bromine or chlorine. The reaction of a compound of general formula (VI) with a compound of general formula (VII) can be carried out in a suitable organic solvent, such as an alcohol, e.g. ethanol, or in dimethylformamide, at a
25 temperature ranging from about 40°C to about 140°C in the

- 10 -

presence of a suitable acid acceptor, e.g. anhydrous potassium carbonate, or triethylamine.

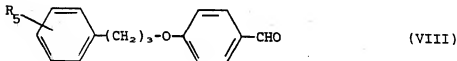
A compound of the invention can be converted, as stated above, into another compound of the invention by known methods.

Also the optional salification of a compound of the invention as well as the conversion of a salt into the free compound and the separation of a mixture of isomers into the single isomers may be carried out by conventional methods.

The compounds of formulae (II) to (VII) are either known compounds or may be obtained according to known methods, e.g. as described in WO-90/14334, or in the Examples which follow.

The compounds of formula (IA) and the pharmaceutically acceptable salts thereof can be obtained by any one of process variants a) to c) described above for the preparation of compounds of formula (I).

The compounds of formula (IA) and the pharmaceutically acceptable salts thereof are preferably obtained by a process comprising reacting a compound of formula (VIII).



wherein R_5 is as defined above; with a compound of

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formula (IX)



and if desired converting a compound of formula (IA) into a pharmaceutically acceptable salt, and/or, if desired, converting a salt into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (IA) into the single isomers.

The reaction of a compound of formula (VIII) with a compound of formula (IX) can be carried out by following the same reaction conditions described above in connection with the reaction of a compound of formula (II) with a compound of formula (III).

Also the additional optional process steps described above as well as the salification of a compound of formula (IA) can be performed according to known methods.

When in the compounds of the present invention and in the intermediate products thereof groups are present, which need to be protected before submitting them to the hereabove illustrated reactions, they may be protected before being reacted and then deprotected, according to methods well known in organic chemistry.

The intermediate compounds, according to the processes herein described for the preparation of the compounds of

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the invention, may be either in the form of a single isomer or as a mixture thereof. Preferably they are in the form of a single isomer.

PHARMACOLOGY

- 5 The compounds of the invention are active on the central nervous system (CNS) and can be used in therapy, for example as antiepileptics, in the treatment of Parkinson's disease and as neuroprotective agents, e.g. in degenerative processes associated with normal ageing
- 10 or pathological situations, such as brain ischemia; they can also be used as antidepressants, hypnotics and antispastic agents. The activity on the CNS of the compounds of the invention was evaluated on the basis of pharmacological methods, such as, for example, the
- 15 antagonism of convulsions and lethality induced by intravenous injection of bicuculline in mice (Antiepileptic Drugs, D.M. Woodbury et al. eds., 2nd edition, Raven Press, New York, 1982), or the antagonism of maximal electroshock seizures (MES) (Woodbury, L.A.
- 20 and Davenport V.D., Arch. Int. Pharmacodyn. Ther. 92; 97-104, 1952).

The neurotoxicity of the compound and of the reference anticonvulsants was assessed with the rotorod test (Dunan and Miye., J. Am. Pharm. Ass. Sci. Ed., 1957, 46, 208;

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Kinnard et al., J. Pharmacol. Exp. Ther. 1957, 121, 354;
Horowitz. Nature, 1963, 200, 369).

For instance, the following Table 1 summarizes the
activity and neurotoxicity data obtained in the MES test
5 and in the rotorod test, respectively, for a
representative group of compounds according to the
present invention, in comparison with the prior art
compound 2-[4-(3-phenylpropyl)oxybenzyl]aminopropanamide
methanesulfonate (internal code FCE 27023) which is known
10 from WO-90/14334

Internal Code FCE	MES-ED ₅₀ (mg/kg)	ROTOROD- TD ₅₀ (mg/kg)	TI
28243	12.4	1005	82
28244	12.5	1011	81
28238	10.6	1581	149
28115	15.9	>2000	>125
28239	14.8	1166	79
28245	8.6	863	100
27023	8.8	584	66

15
20 wherein:

ED₅₀ means effective dose in 50% of treated animals

TD₅₀ means toxic dose in 50% of treated animals

TI means therapeutic index (TD₅₀/ED₅₀)

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FCE 28243 means 2-{4-[4-phenylbutyl]oxybenzyl}amino-propanamide, methanesulfonate

FCE 28244 means 2-{4-[5-phenylpentyl] oxybenzyl}amino-propanamide, methanesulfonate

5 FCE 28238 means 2-{4-[3-chlorophenyl]propyl]oxybenzyl}aminopropanamide, methanesulfonate

FCE 28115 means 2-{4-[3-fluorophenyl]propyl]oxybenzyl}aminopropanamide, methanesulfonate

10 FCE 28239 means 2-{4-[3-chlorophenyl]propyl]oxybenzyl}aminopropanamide, methanesulfonate

FCE 28245 means 2-{4-[3-phenylpropyl]oxybenzyl}amino-3-hydroxy-propanamide, methanesulfonate.

From the above comparative test data it is evident that the compounds of the present invention are endowed with a better therapeutic index than the prior art compounds.

15 A patient is treated according to the present invention by a method comprising administering to the patient an effective amount of one of the compounds of the invention. In this way the present compounds can be used

20 to treat disorders of the central nervous system, for example epilepsy or Parkinson's disease; or as neuroprotective agents, anti-depressants, hypnotics or anti-spastic agents. The condition of a patient may thus be improved.

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The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions; rectally, in the form of suppositories; 5 parenterally, e.g. intramuscularly or by intravenous injection or infusion. The therapeutic regimen for the different clinical syndromes must be adapted to the type of pathology taking into account, as usual, also the route of administration, the form in which the compound 10 is administered and the age, weight and conditions of the subject involved.

The oral route is employed, in general, for all conditions requiring such compounds. In emergency situations preference is given to intravenous injection. 15 For these purposes the compounds of the invention can be administered orally at doses ranging e.g. from about 20 to about 1500 mg/day. Of course, these dosage regimens may be adjusted to provide the optimal therapeutic response.

20 The nature of the pharmaceutical composition containing the compounds of this invention in association with pharmaceutically acceptable carriers or diluents will, of course, depend upon the desired route of administration. The composition may be formulated in the conventional 25 manner with the usual ingredients. For example, the compounds of the invention may be administered in the

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form of aqueous or oily solutions or suspensions, tablets, pills, gelatine capsules, syrups, drops or suppositories.

Thus, for oral administration, the pharmaceutical compositions containing the compounds of this invention are preferably tablets, pills or gelatine capsules which contain the active substance together with diluents, such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, for instance silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; or they may also contain binders, such as starches, gelatine, methylcellulose, carboxymethyl-cellulose, gum arabic, tragacanth, polyvinylpyrrolidone; disaggregating agents, such as starches, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example by means of mixing, granulating, tableting, sugar-coating or film-coating processes.

The liquid dispersions for oral administration may be, e.g., syrups, emulsions and suspensions.

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The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

5 The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspensions or solutions for intramuscular injections may contain together with the active compound a
10 pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injection or infusion may
15 contain as carrier, for example, sterile water or preferably they may be in the form of sterile aqueous isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g.
20 cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the invention.

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Example 1

Diethyl 2-(2-fluorobenzyl)malonate

5.6 g (0.0243 g.a.) of metal sodium were carefully dissolved in abs. EtOH (145 ml) under a nitrogen atmosphere. At the end of the dissolution, 62 ml (0.408 mol) of diethylmalonate and 26.9 ml (0.205 mol) of 2-fluorobenzylchloride were added. The mixture was kept at 50°C for 5 hours, then cooled to room temperature and allowed to stand overnight. After evaporation, the crude residue was taken up with water and extracted with ethyl acetate. The extracts were washed with brine and dried over an. sodium sulfate. The crude oil obtained after evaporation was distilled at 132°C/0.8 mm/Hg to provide 49 g (73%) of diethyl 2-(2-fluorobenzyl)malonate.

15 Example 2

3-(2-fluorophenyl)propionic acid

49 g (0.183 mol) of diethyl 2-(2-fluorobenzyl)malonate were mixed with 183 ml of 37 % HCl and 9.4 ml of glacial acetic acid. The mixture was heated at reflux for 27 hours, then cooled; the solid precipitated was filtered, taken up with water, basified with sat. NaHCO₃, washed with diethyl ether, then reacidified with 20 % HCl,

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extracted with diethyl ether and washed with brine. After drying and evaporation, the oily residue was taken up with petroleum ether: upon freezing a white solid precipitated (21.5 g; 70 %).

5 Example 3

3-(2-fluorophenyl)propan-1-ol

21 g (0.125 mol) of 3-(2-fluorophenyl)propionic acid were dissolved in THF. While stirring and cooling at 0°C, under a nitrogen atmosphere, 11.8 g (0.311 mol) of sodium borohydride were added, and 78 ml (0.636 mol) of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ dropped. Stirring at 0°C was continued for 1 h, then, 200 ml of (1:1) water:methanol were carefully added. The mixture was evaporated, taken up with water, extracted with ethyl acetate; the organic phase was washed with 15 brine, dried and evaporated. The crude oil obtained was flash-chromatographed on silica gel (eluant: chloroform 190 - methanol 10) to furnish a colorless fluid (12.8 g; 67%).

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Example 4

3-(2-fluorophenyl)propyl methanesulfonate

12.7 g of 3-(2-fluorophenyl)propan-1-ol (0.0824 mol) were dissolved in CH_2Cl_2 (250 ml) and the mixture was kept to 5°C, under nitrogen. 11.5 ml of triethylamine were added, followed by 6.35 ml of methanesulfonyl chloride in CH_2Cl_2 (20 ml) while maintaining the temperature at 5°C. The mixture was kept to room temperature, washed with brine; the organic phase was dried and evaporated to give an oil (18.5 g; 97%).

Example 5

4-(3-(2-fluorophenyl)propyl)oxybenzaldehyde

To a suspension of 55 % sodium hydride (3.34 g; 0.08 mol) in DMF (180 ml), at room temperature under nitrogen, 9.7 g (0.08 mol) of 4-hydroxybenzaldehyde were added; the mixture was heated to 50°C, then 18.5 g (0.08 mol) of 3-(2-fluorophenyl)propyl methanesulfonate in 20 ml of DMF were dropped. The temperature was kept to 70°C and maintained for 1 hour. The solvent was removed, the residue taken up with water, extracted with ethyl acetate, washed with brine, dried over an. Na_2SO_4 , evaporated to provide an oil which was further purified

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by flash-chromatography on silica gel (eluant: cyclohexane 8 : ethyl acetate 2). A colourless oily residue was obtained (15 g; 73 %).

Example 6

- 5 (S)-2-[4-(3-(2-fluorophenyl)propyl)oxybenzyl]amino-propionamide

To a solution of (S)-(+)-2-aminopropanamide (1.93 g; 0.0170 mol) in anhydrous methanol (60 ml), under stirring and nitrogen, 2.0 g of 4Å molecular sieves were added and
10 then, in a single portion, NaBH₃CN (0.78 g; 0.0124 mol); after 10 minutes, 4 g (0.0155 mol) of 4-(3-(2-fluorophenyl)propyl)oxybenzaldehyde were added, in 20 ml of anhydrous methanol. After 3 hours, the reaction was completed, the mixture was filtered, the filtrates washed
15 with methanol, the residue was directly flash-chromatographed on silica gel (eluant: CH₂Cl₂ 195: CH₃OH 5: 30 % NH₄OH 0.5) to give a white solid (2.7 g; 53 %). The free base thus obtained was treated with a stoichiometric amount of methanesulfonic acid to yield
20 (S)-(+)-2-[4-[3-(2-fluorophenyl)propyl)oxybenzyl]amino-propanamide, methanesulfonate; m.p. 172-177°C; $[\alpha]_D^{25} +10.4$ (C=1.06, AcOH).

Analogously, starting from the same aldehyde and (R)-(+)-

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2-aminopropanamide, the R-enantiomer of the title compound can be obtained; m.p. 177-180°C; $[\alpha]_D^{25}$ -11.5 (C=1.09, AcOH).

Analogously, the following compounds can be obtained
5 starting from the appropriate aldehyde and (R) or (S)- α -aminoamide either in the (S)- or (R)- enantiomeric form.

2-{4-[3-(3-fluorophenyl)propyl]oxybenzyl}aminopropanamide
methanesulfonate; m.p. 150-152°C

10 2-{4-[2-(2-fluorophenyl)ethyl]oxybenzyl}aminopropanamide
methanesulfonate; m.p. 176-180°C

2-{4-[2-(3-fluorophenyl)ethyl]oxybenzyl}aminopropanamide
methanesulfonate; m.p. 165-168°C

2-{4-[5-phenylpentyl]oxybenzyl}aminopropanamidemethane-
15 sulfonate; m.p. 162-165.5°C

2-{4-[4-phenylbutyl]oxybenzyl}aminopropanamide methane-
sulfonate; m.p. 165-168°C

2-{4-[3-(4-fluorophenyl)propyl]oxybenzyl}aminopropanamide
methanesulfonate; m.p. 173-176°C

20 2-{4-[3-(2-chlorophenyl)propyl]oxybenzyl}aminopropanamide
methanesulfonate; m.p. 170°C (dec.)

2-{4-[3-(3-chlorophenyl)propyl]oxybenzyl}aminopropanamide
methanesulfonate; m.p. 152.5-155°C

2-{4-[3-(4-chlorophenyl)propyl]oxybenzyl}aminopropanamide
25 methanesulfonate;

2-{4-[3-(2-bromophenyl)propyl]oxybenzyl}aminopropanamide

- methanesulfonate; m.p. 171-173°C (dec.)
- 2-{4-[3-(3-bromophenyl)propyl]oxybenzyl}aminopropanamide
methanesulfonate; m.p. 140°C (dec.)
- 2-{4-[3-(2,6-dichlorophenyl)propyl]oxybenzyl}aminopropan-
5 amide methanesulfonate;
- 2-{4-[3-(3-methoxyphenyl)propyl]oxybenzyl}aminopropan-
amide methanesulfonate; m.p. 154-156.5°C
- 2-{4-[3-(2-methoxyphenyl)propyl]oxybenzyl}aminopropan-
amide methanesulfonate; m.p. 127.5-129.5°C
- 10 2-[4-(3-phenylpropyl)oxybenzyl]amino-3-hydroxy-propan-
amide methanesulfonate; m.p. 115°C (dec.)
- 2-{4-[3-(2-fluorophenyl)propyl]oxybenzyl}amino-3-hydroxy-
propanamide methanesulfonate;
- 2-{4-[3-(3-fluorophenyl)propyl]oxybenzyl}amino-3-hydroxy-
15 propanamide methanesulfonate; and
- 2-[4-(3-phenylpropyl)oxybenzyl]amino-3-hydroxy-N-methyl-
propanamide methanesulfonate; m.p. 95-101°C

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Example 7

Tablets, each weighing 300 mg and containing 100 mg of active substance can be manufactured as follows:

Composition (for 5000 tablets)

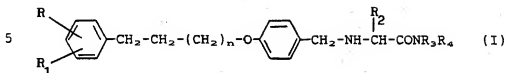
5	2-{4-[3-(3-fluorophenyl)propyl]oxybenzyl}	
	aminopropanamide methanesulfonate	500 g
	Lactose	710 g
	Corn starch	237.5 g
	Talc powder	37.5 g
10	Magnesium stearate	15 g

2-{4-[3-(3-fluorophenyl)propyl]oxybenzyl}aminopropanamide methanesulfonate hydrochloride, lactose and half of the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (18 g) is
15 suspended in warm water (180 ml).

The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve of sieve size 1.4 mm, then the remaining quantity of starch, talc and magnesium is added, carefully mixed, and processed into
20 tablets.

CLAIMS

1. A compound of formula (I)



wherein

n is zero or an integer of 1 to 3;

each of R and R₁, which may be the same or different, is hydrogen, halogen, trifluoromethyl or C₁-C₄ alkoxy;

10 R₂ is hydrogen or C₁-C₄ alkyl optionally substituted by hydroxy;

each of R₃ and R₄ independently is hydrogen or C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof;

and wherein when, at the same time, n is zero, 1 or 2,

15 R₂ is hydrogen or unsubstituted C₁-C₄ alkyl and R and R₁ are as defined above, then R₃ and R₄ are both hydrogen; and wherein when, at the same time, R and R₁ are hydrogen, n is zero and R₂ is methyl, then at least one of R₃ and R₄ is other than hydrogen.

20 2. A compound of formula (I), according to claim 1, wherein

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n is as defined in claim 1;

R is hydrogen and R₁ is hydrogen, halogen or C₁-C₄ alkoxy;

R₂ is C₁-C₄ alkyl; and

5 R₃ and R₄ are hydrogen; or a pharmaceutically acceptable salt thereof.

3. A compound which is

2-{4-[2-(2-fluorophenyl)ethyl]oxybenzyl}aminopropanamide;

10 2-{4-[2-(3-fluorophenyl)ethyl]oxybenzyl}aminopropanamide;

2-{4-(4-phenylbutyl)oxybenzyl}aminopropanamide;

2-{4-[3-(2-fluorophenyl)propyl]oxybenzyl}aminopropanamide;

15 2-{4-[3-(3-fluorophenyl)propyl]oxybenzyl}aminopropanamide;

2-{4-[3-(4-fluorophenyl)propyl]oxybenzyl}aminopropanamide;

20 2-{4-[3-(2-chlorophenyl)propyl]oxybenzyl}aminopropanamide;

2-{4-[3-(3-chlorophenyl)propyl]oxybenzyl}aminopropanamide;

2-{4-[3-(4-chlorophenyl)propyl]oxybenzyl}aminopropanamide;

25 2-{4-[3-(2-bromophenyl)propyl]oxybenzyl}aminopropan-

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amide;

2-[4-(5-phenylpentyl)oxybenzyl]aminopropanamide;

2-[4-[3-(3-bromophenyl)propyl]oxybenzyl]aminopropanamide;

5 2-[4-[3-(2,6-dichlorophenyl)propyl]oxybenzyl]aminopropanamide;

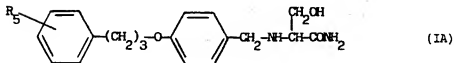
2-[4-[3-(3-methoxyphenyl)propyl]oxybenzyl]aminopropanamide;

10 2-[4-[3-(2-methoxyphenyl)propyl]oxybenzyl]aminopropanamide;

2-[4-(3-phenylpropyl)oxybenzyl]amino-3-hydroxy-N-methylpropanamide;

if the case, either as single (S) or (R) isomer or as
a mixture thereof; or a pharmaceutically acceptable
15 salt thereof.

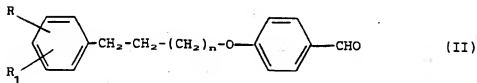
4. A compound of formula (IA)



wherein R₅ is hydrogen, halogen, trifluoromethyl or
C₁-C₄ alkoxy; or a pharmaceutically acceptable salt
20 thereof.

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5. A compound of formula (IA) according to claim 4 wherein R_3 is hydrogen or halogen; or a pharmaceutically acceptable salt thereof.
6. A compound which is
- 5 2-[4-(3-phenylpropyl)oxybenzyl]amino-3-hydroxy-propanamide;
- 2-[4-[3-(2-fluorophenyl)propyl]oxybenzyl]amino-3-hydroxy-propanamide;
- 2-[4-[3-(3-fluorophenyl)propyl]oxybenzyl]amino-3-
- 10 hydroxy-propanamide;
- if the case, either as single (R) or (S) isomer or as a mixture thereof; or a pharmaceutically acceptable salt thereof.
7. A process for the preparation of a compound of formula
- 15 (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, the process comprising
- a) reacting a compound of formula (II)

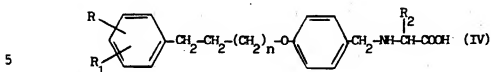


- wherein R, R_1 and n are as defined in claim 1, with a
- 20 compound of formula (III)

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wherein R_2 , R_3 and R_4 are as defined in claim 1; or
 b) reacting a compound of formula (IV) or a reactive derivative thereof

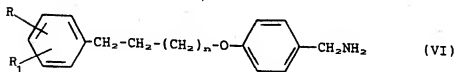


wherein R , R_1 , n and R_2 are as defined in claim 1,
 with an amine of formula (V)



wherein R_3 and R_4 are as defined in claim 1; or

10 c) reacting a compound of formula (VI)



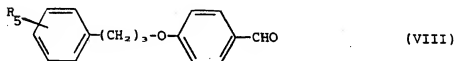
- 30 -

wherein R, R₁ and n are as defined in claim 1, with a compound of formula (VII)



5 wherein R₂, R₃ and R₄ are as defined in claim 1 and W is a halogen atom; and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, converting a compound of the invention into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free
10 compound and/or, if desired, separating a mixture of isomers of compounds of the invention into the single isomers.

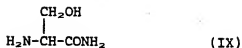
8. A process for the preparation of a compound of formula
15 (IA), or a pharmaceutically acceptable salt thereof, as defined in claim 4, the process comprising reacting a compound of formula (VIII)



wherein R₅ is as defined in claim 4, with a compound

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of formula (IX)

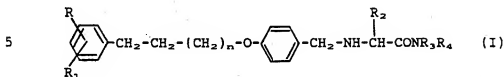


- 5 and, if desired, converting a compound of formula (IA) into a pharmaceutically acceptable salt, and/or, if desired, converting a salt into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (IA) into the single isomers.
- 10 9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I) or (IA) as defined in any of claims 1 to 6 or a pharmaceutically acceptable salt thereof.
- 15 10. A compound of formula (I) or (IA), as defined in claim 1 or 4, or a pharmaceutically acceptable salt thereof, for use as an anti-epileptic, anti-Parkinson, neuroprotective, antidepressant, antispastic or hypnotic agent.

AMENDED CLAIMS

[received by the International Bureau on 28 July 1994 (28.07.94);
original claim 1 amended;
other claims unchanged (1 page)]

1. A compound of formula (I)



wherein

n is zero or an integer of 1 to 3;

each of R and R₁, which may be the same or different,
10 is hydrogen, halogen, trifluoromethyl or C₁-C₄ alkoxy;
R₂ is hydrogen or C₁-C₄ alkyl optionally substituted
by hydroxy;

each of R₃ and R₄ independently is hydrogen or C₁-C₄
alkyl; or a pharmaceutically acceptable salt thereof;
15 and wherein when, at the same time, n is zero, 1 or 2,
R₂ is hydrogen or unsubstituted C₁-C₄ alkyl and R and
R₁ are as defined above, then R₃ and R₄ are both
hydrogen; and wherein when, at the same time, R and R₁
are hydrogen, n is zero or 1 and R₂ is methyl, then at
20 least one of R₃ and R₄ is other than hydrogen.

2. A compound of formula (I), according to claim 1,
wherein

STATEMENT UNDER ARTICLE 19

The amendment made in claim 1 is clearly a correction of a clerical error, indeed the correct statement finds its counterpart at page 3 lines 2 and 3 of the specification. The amendment made in claim 1 does not add any new matter to the invention, therefore it has not any impact on the description as filed.

INTERNATIONAL SEARCH REPORT

Initial Application No

PCT/EP 94/00802

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C237/06 A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 90 14334 (FARMITALIA CARLO ERBA) 29 November 1990 cited in the application see page 33, line 5, page 34, line 1; claims 1, 2, 5, 6 -----	1, 2, 4, 5, 9, 10

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

2 June 1994

Date of mailing of the international search report

13.06.94

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Seufert, G

INTERNATIONAL SEARCH REPORT

Information on patent family members

Initial Application No

PCT/EP 94/00802

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9014334	29-11-90	AU-B- 645752	27-01-94
		AU-A- 5729990	18-12-90
		CN-A- 1047496	05-12-90
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		DE-T- 69004337	24-02-94
		EP-A- 0400495	05-12-90
		EP-A- 0426816	15-05-91
		JP-T- 4500215	16-01-92
		US-A- 5276611	04-01-94
		US-A- 5236957	17-08-93
